

**HYPOTH - Gene Environment Folate April 5, 2002.**

NCS hypothesis submission

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**Folate status in early pregnancy**

1) Hypothesis: Specific alleles for genes involved in folate metabolism predispose women who are pregnant and who have had low folate intake over the six months preceding conception to have a fetus at increased risk for birth defects. Environmental contributors to this can best be measured with nutritional survey data collected as close to the time of conception as possible and with the collection of maternal blood samples in early pregnancy that assess folate status. Maternal genetic contributors can best be measured by having DNA samples from the infant, both parents and both maternal grandparents.

The National Children's Study will provide a unique opportunity to Collect data necessary to address the above hypothesis. First collection of questionnaire data regarding maternal nutrition as well as assays of folate status of the mother in early pregnancy are critical to this study. The NCS will have contact with mothers in early pregnancy when recall bias for the nutrition information will be at a minimum. Similarly the ability to collect biological samples in early pregnancy will allow for direct measurement of maternal folate status at the critical time for fetal development. Finally collection of DNA samples from infant, parents and maternal grandparents will allow for study designs such as the transmission disequilibrium test (TDT) that examines the mothers allelic variants as the risk alleles as well as the infants alleles. Since it is the maternal folate status that is the risk factor having the mothers parents allows one to examine transmission distortion of risk alleles to the mother directly.

2) Design issue for clarification

Two design issues need clarification for evaluation of this hypothesis by the NCS.

a) Can mothers be identified within the first 3 months of pregnancy, interviewed and blood samples collected for red cell folate and other indicators of folate status.

b) Will the family units be available for study including collection of samples for DNA from infants, both parents and the mothers parents.

3) Pilot study draft

To evaluate the feasibility of this study pilot data on what proportion of women who can be successfully enrolled in the study will be required using at least two representative demographic groups. Possible groups for study could include rural populations, inner city populations, underrepresented groups such as minority populations or non-English speaking populations or teenaged mothers. Each group would have a minimum of 200 consecutive new patients in the relevant practice or

clinic setting contacted and attempts at enrolment made. Success in contact, collection of informed consent, successful completion of demographic, nutritional survey and family history data forms, collection of blood for biological assays from the mother (and her stage of pregnancy), identification of the father and maternal grandparents and the success in enrolling them and collection of their DNA samples could be examples of benchmarks for achievable milestones. Comparison between groups and to a reference population would provide a range of success in the different groups. Minimum standards for participation at each phase should be suggested. Consideration could be given to developing focus groups to determine factors that limited participation in certain groups as well.

4) Working groups that might interact would include

Birth defects

Community outreach and communications

Ethics

Exposure to chemical agents

Fertility and early pregnancy

Gene-environment interactions

Health disparities and environmental justice

Health services

IT

Medicine and pharmaceuticals

Recruitment and retention

Repository

Social environment

Study design